**REMARKS**

Following entry of the present amendment, claims 33, 35, and 36 remain in the application for consideration. Claims 1-32, 34, 37-66 were previously cancelled without prejudice. No new matter is added herewith.

Rejections under 35 USC §112, First Paragraph

Claims 33 and 35-36 stand rejected under 35 USC §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

Contrary to the assertion of the outstanding Office Action that claim 33 is too broad, Applicants point out that claim 33 is limited to the presence of alternation of three specific amino acids 564-566 of SEQ ID NO 4 or fragments thereof comprising SEQ ID NO 5 and 6, which both have these amino acids altered. However, to facilitate the prosecution of the application, Applicants herein amend claim 33 to add the limitation of "by monitoring an inhibition or activation of transactivation/degradation of HIF-1 alpha" to the step of detecting the binding affinity of the isolated protein to the target protein to determine an agent-biased affinity. Support for the amendment may be found in paragraph 26 of the instant application. Applicants now submit that there is sufficient

disclosure in the specification to teach one of skill in the art to perform the method of screening for an agent as recited in the instantly amended claims.

Particularly, and contrary to the position taken by the Office Action, claim 33 is consistent and well supported by the specification regarding abrogating interaction/affinity between PYI and the VHL protein.

Applicants direct the Examiner's attention to paragraphs 26 to 32 where SEQ ID NO 5 and 6 comprising amino acids 564-566 are discussed.

Paragraphs 26 and 27 disclose the degradation/transactivation of HIF-1 alpha:

> [0026] The invention provides a screening system for identifying agents that affect the degradation/ transactivation of HIF-1 alpha. The screening system comprises preparing and admixing a substantially purified preparation of a polypeptide having at least an amino acid of SEQ ID NO: 5 (minimum N-TAD) or a smaller fragment thereof (SEQ ID NO : 6 (residues 547-575; Fig. 28)) or described mutants thereof with a test agent; and monitoring, by any suitable means, an inhibition of transactivation of HIF-1 alpha, whereby an inhibition of the transactivation of HIF-1 alpha identifies an HIF-1 alpha antagonist. This screening system can also be used to identify agents which activate the transactivation of HIF-1 alpha.
>
> [0027] Based on substantial over expression in mammalian cells of a polypeptide having at least an amino acid of SEQ ID NO: 5 (minimum N-TAD) or a smaller fragment thereof (SEQ ID NO: 6 (residues 547-575; Fig. 28)) or described mutants thereof

> and the VHL protein (SEQ ID NO: 2) the screen system functions under normoxic conditions to monitor alteration of the transactivation potential of the domain described in SEQ ID NOs: 5 or 6, or their protein stability (degradation) by agents.

Paragraph 0028 states that the transactivation/degradation of HIF-1 alpha (SEQ ID NO 4 normal without the PYI alteration of amino acids 564-566) may be altered.

> [0028] Use of this screen system provides a means to determine agents/compounds that may alter the transactivation/degradation of HIF-1 alpha. This screening method may be adapted to large-scale, automated procedures such as a PANDEX (Baxter-Dade Diagnostics) system, allowing for efficient high-volume screening of potential therapeutic agents.

Further, paragraph 0030 and 0032 disclose "affecting or modulating its activity or function" and "a difference in activity between the treated and untreated polypeptides is indicative of a modulating effect":

> [0030] A polypeptide according to the present invention may be used in screening for molecules which affect or modulate its activity or function. Such molecules may be useful in a therapeutic (possibly including prophylactic) context.
>
> [0032] A method of screening for a substance which modulates activity of a polypeptide may include contacting one or more test substances with the polypeptide in a suitable reaction medium, testing the activity of the treated polypeptide and comparing that activity with the activity of the

polypeptide in comparable reaction medium untreated with the test substance or substances. A difference in activity between the treated and untreated polypeptides is indicative of a modulating effect of the relevant test substance or substances.

Moreover, claim 33 recites reference affinity and difference between affinities:

Claim 33: A method of screening for an agent which modulates the function of a protein comprising the amino acid sequence of SEQ ID NO:5, comprising
incubating a mixture comprising:
an isolated protein comprising the amino acid of SEQ ID NO:4 (HIF-1 alpha) with an altered PYI motif at residues 564-566 or a fragment thereof comprising SEQ ID NO:5 or SEQ ID NO:6;
the sequence of SEQ ID NO:2; and
a candidate agent under conditions whereby, but for the presence of said agent, said isolated protein mediates VHL-dependent degradation or physically interacts with VHL at a reference affinity;
detecting the binding affinity of said isolated protein to SEQ ID NO:2 to determine an agent-biased affinity by monitoring an inhibition or activation of transactivation/degradation of HIF-1 alpha;
wherein a difference between said reference affinity and said agent-biased affinity indicates that said agent modulates the functional activity of said isolated protein to said sequence of SEQ ID NO:2.

It is therefore submitted that the description very well teaches that the affinity between SEQ ID NO:4 with an altered PYI motif at residues 564-566 of SEQ ID NO 4 or fragments thereof comprising SEQ ID NO 5 and 6 and VHL (SEQ ID NO: 2) may

be altered by an agent. This may result in a difference in degradation of SEQ ID NO: 2 and in a difference in the amount of unaffected SEQ ID NO: 2.

Applicants submit that claim 33 and the claims depending from it are in compliance with the enablement requirement and are now in condition for allowance. A Notice of Allowance is eagerly solicited.

Any fees due with this request may be charged to Deposit Account 23-1665, Customer Number 27267.

If the Examiner has any questions or feels that a discussion with Applicants' representative would expedite prosecution, the Examiner is invited and encouraged to contact Applicants' undersigned representative at the telephone number listed below.

Respectfully submitted,

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